A decade ago, 3 potentially groundbreaking trials were published that ushered in a new era of cardiovascular regenerative medicine. Using autologous bone marrow mononuclear cells (BMCs) in patients with acute ST-segment–elevation myocardial infarction (STEMI), the trials were notable for their clear signal of safety, but discordant in their findings of benefit. Unfortunately, the 1-year results of the SWISS-AMI trial (Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction) reported in this issue of Circulation Research again remind us about the inability of BMC therapy in patients with STEMI to demonstrate consistent benefit. Why are there such disparate results in trials using a similar cell product in a similar patient population?

REPAIR-AMI (Reinfusion of Enriched Progenitor cells and Infarct Remodeling in Acute Myocardial Infarction), remains the largest (n=204) and landmark trial to demonstrate that BMCs improve left ventricular (LV) function in patients after STEMI. Patients were randomized to intracoronary delivery (using stop-flow technique) of BMC versus placebo 3 to 7 days after successful percutaneous coronary intervention (PCI). At 4 months, BMC-treated patients had a significant improvement in ejection fraction (EF) measured by left ventriculography at 4 months compared with placebo (5.5±7.3% versus 3.0±6.5%; P=0.01). In subgroup analyses, the improvement in LVEF was most significant in patients with a baseline LVEF below the median value of 48.9% and in patients treated ≥4 days post MI. At 1 year, there was a significant reduction in the prespecified combined clinical end point of death, recurrent MI, and any revascularization procedure (5.8% versus 1.9%; P=0.01). This trial generated excitement for the potential of cardiovascular stem cell therapy for AMI (as well as other cardiovascular diseases), but this excitement was tempered by the results of a second study, ASTAMI (Autologous Stem cell Transplantation in Acute Myocardial Infarction), published in the same issue of the NEJM, which demonstrated no change in LVEF by nuclear imaging, echo, or magnetic resonance imaging (MRI) in 97 patients treated with intracoronary BMC versus placebo a median of 6 days post AMI. In addition, several months earlier, investigators from Belgium had reported no improvement in LVEF at 4 months by MRI in 67 STEMI patients treated within 24 hours of successful PCI with intracoronary BMC versus placebo but found that the BMC-treated patients had a reduction in myocardial infarct size and better recovery of regional systolic function. The negative impact of microvascular obstruction (present in 50%) was also apparent, but unfortunately it was not influenced by treatment with BMC.

Now, 10 years later, the investigators from the SWISS-AMI trial report the 12-month results of 200 patients randomized to open-label control compared with early treatment (5–7 days) or late treatment (3–4 weeks) post MI with BMCs. Consistent with the previously reported SWISS-AMI 4-month results and the 6-month results of the National Institutes of Health (NIH) sponsored TIME and Late TIME trials, there were no significant improvement in LVEF by MRI at 12 months (−1.9±1.8% for control, −0.09±10.5% for early treatment, and −0.7±10.1% for late treatment groups). Also similar to TIME and Late TIME, there was no difference in clinical events.

There have been nearly as many meta-analyses as there have been clinical trials, and their interpretation is often complicated by the inclusion of both acute and chronic ischemic heart disease, multiple cell types, and various methods of delivery. A recent meta-analysis including only intracoronary BMC for AMI (1641 patients from 16 studies) reported a modest improvement in LVEF (2.55% increase) and a reduction in LV volumes that was more pronounced in younger patients. Another meta-analysis published nearly the same time included 30 trials (22 with BMC) comprising 2037 patients with AMI. These authors reported a 2.1% absolute improvement in LVEF with BMC therapy and modest improvements in volumes and infarct size but no beneficial effect on clinical events. In contrast, a patient-level meta-analysis with 1252 patients from 12 trials found no difference in major adverse cardiac effects, LVEF, or volumes. Why the consistently inconsistent results?

1. The inherent limitations of autologous BMC: The major limitation of autologous BMC may be the considerable patient-to-patient variability related to a decrease in the number and potency of stem cells that occurs with age and cardiovascular risk factors. This was apparent in the

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Delewí meta-analysis and well-illustrated in the NIH FOCUS trial (First Mononuclear Cells injected in the United States) using intramyocardial BMC in patients with chronic ischemic heart failure. Overall, there was a 2.7% improvement in LVEF in BMC-treated patients. Importantly, patients who were either (1) younger or (2) had a greater number of CD34+ cells had a greater increase in LVEF during the course of the trial, demonstrating the importance of a specific patient’s cell product.

2. The dynamic nature of the condition: After STEMI, there is well-documented upregulation and downregulation of a large number cytokines, growth factors, and inflammatory factors. These dynamic cellular changes occur in the setting of improving LVEF over time after successful reperfusion because of resolution of myocardial stunning. Fluctuating changes in both the baseline LVEF measurement and the biological environment make it challenging to detect a cell-based efficacy signal in the presence of this background variability.

3. A not-so-gold standard measure of LV function: Although it is widely thought that MRI is the gold standard for the measurement of LVEF, volumes and infarct size, MRI has many important limitations, including the difficulty distinguishing true infarct from myocardial edema and the significant dropout related to claustrophobia and implantation of defibrillators and pacemakers commonly required in a post-AMI with LV dysfunc-tion patient population. SWISS-AMI nicely illustrates this limitation with the 25% lost to MRI follow-up rate, which was similar to the 15% at 1 year in the TIME trial. Also, the considerable changes in technology during the last decade and intercenter variability in technique and analysis make MRI less than a gold standard.

4. The changing natural history of the disease: There has been a dramatic improvement in the clinical outcome of STEMI primarily related to the increased availability of timely reperfusion with PCI and the subsequent growth of regional STEMI systems throughout the world. This is illustrated by the 5.4% 2-year mortality in REPAIR-MI compared with the overall 2-year mortality of 2.3% in SWISS-AMI and <1% at 1 year in TIME, both of which enrolled predominantly high-risk anterior MI patients. It will be challenging to show a mortality difference with rates <3%, even in selected high-risk patients with LVEF <45%. It is sobering that the 3000-patient BAMI trial (The Effect of Intracoronary Reinfusion of BMC on All Cause Mortality in Acute Myocardial Infarction; NCT01569178) was initially powered for a 12% mortality in LVEF in BMC-treated patients. Importantly, patients who were either (1) younger or (2) had a greater number of CD34+ cells had a greater increase in LVEF during the course of the trial, demonstrating the importance of a specific patient’s cell product.

5. The BMC processing controversy: Although processing of autologous BMC by density centrifugation is theoretically straightforward and inexpensive, there has been a great deal of controversy about the influence of RBCs, the presence of heparin, and processing techniques (Ficoll, Lymphoprep, Sepax). These issues exacerbate the small sample sizes and inherent patient variability.

6. The high expectations for the field of cell therapy: The unmitigated (or unbridled) enthusiasm for the potential of cell therapy in the press has created unrealistic expectations in the lay public. This combined with the controversy within the scientific community with those who think that the clinical trials are not warranted, and the proliferation of commercial stem cell centers outside and inside the United States, have provided a challenging if not inimical environment for adequately powered clinical trials.

7. Funding for an adequately powered clinical trial: Absence of a successful business model challenges the provision of sufficient funding for well-powered clinical trials especially with BMC. It is worth remembering that it took 41021 patients enrolled in the GUSTO trial (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) to show a mortality difference of 6.3% with tissue plasminogen activator versus 7.4% with streptokinase reperfusion. It is enlightening to realize the largest trial assessing cell therapy post AMI to date remains the 204-patient REPAIR-AMI trial with the second largest being the 200-patient SWISS-AMI trial 10 years later. Despite the success of the REPAIR-AMI trial and the excitement it generated, the design, initiation, and successful completion of the BAMI trial without the benefit of industry support would be a monumental accomplishment.

8. Accurate identification of high-risk patients: Despite the dramatic improvement in the natural history of STEMI, there are still high-risk patients. Appropriate selection remains the challenge. High-risk patients frequently present with out-of-hospital cardiac arrest or advanced cardiogenic shock and are not well suited for clinical trials. LVEF alone is inadequate (especially early) because of myocardial stunning. The presence of microvascular obstruction seems to identify a high-risk patient population but requires an MRI before enrollment. The index of microcirculatory resistance may be a marker of microvascular obstruction but requires further study.

9. Inadequate potency of BMC: Even in ideal circumstances, unselected BMC may represent a relatively impotent cell product, with limited potential for improving EF or clinical outcomes in patients with AMI. Thus, the discrepant findings likely reflect small treatment effects in relatively underpowered studies. This reality has stimulated many alternative approaches, including allogeneic cells, enhanced or selected autologous cells, and cardiac-derived stem cells.

More than a decade after the initial groundbreaking trials, we are still attracted to the potential and simplicity of BMC for the treatment of patients surviving a large AMI, but now know from experience how difficult this challenge has proven to be. Certainly, considerable knowledge has been gained and we anticipate the results of BAMI, the first adequately powered phase 3 trial but the reality of a cell-based therapy for AMI may be a challenge that remains unmet.

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Consistently Inconsistent—Bone Marrow Mononuclear Stem Cell Therapy Following Acute Myocardial Infarction: A Decade Later
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